Author's response to reviews

Title: Cardiovascular autonomic function tests in an African population: A report on reference values

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Author's response to reviews: see over
Dear Editor

Many thanks for the reviewers’ comments. We have read their comments thoroughly. Please find the reviewers’ comments in bold print, our response in italic print below, and changes made in the revised manuscript written in red print.

Reviewer 1:

A separate Limitation section should be created in which some problems should be mentioned including the followings: the patient number is not really high (only 276), so only suggestions in the Conclusion can be given. Especially when different aged mini-populations are compared (from 29 to 71) (see Tables).

I think to give reference values from a mixed African population (<300 patients !) are too strong messages!

We agree with the reviewer, even though the current reference values by Ewing are based on fewer subjects, establishing population specific reference values needs a larger and broader population. We have taken the comment into consideration and have removed “reference values” from the title. We have also made a changes accordingly in the conclusion of the abstract (page 2) and in the conclusion of the manuscript (on page 12, paragraph 2).

It is always a problem who is healthy: I personally miss the consideration of hypercholesterolaemia and other laboratory findings in the statistical evaluations.

As listed in the exclusion criteria (page 4, paragraph 3), beside of asking about diseases, we assessed for neurological abnormalities, hypertension, known alcohol addiction, anaemia, and chronic diseases of importance (DM, renal failure, tuberculosis, asthma, chronic obstructive pulmonary diseases, and peptic ulcer). Testing for hypercholesterolemia would not have been feasible because of lacking laboratory facilities in this resource poor setting where the study was conducted.

Reviewer 2:

Ethnic differences in blood pressure have been found between the tribes. What are possible reasons for this? (environment, genetic, habits,).

We have not found any other studies describing ethnic difference in blood pressure between Bantoids and other tribes. Reasons might be different genetic make ups and/or life style
determinants. We suggest that these determinants need to be further assessed (page 9, paragraph 2 and page 10, paragraph 1).

What about height and weight differences between the groups? Please provide height and weight of the studied population.

Height and weight could have been assessed, but was unfortunately not included in the protocol. This is a weakness of our study.

The authors should discuss the limitation of this study. They should describe how diet and drugs were controlled during the study.

None of the subjects was on any medication at the time of the study (page 4, paragraph 3). The test battery was all together completed within approximately 30 minutes. Each subject was asked when they last had their meal, since meals within shorter time than 2 hours may affect the test result in terms of postprandial hypotension. No diet history was taken. From our knowledge the staple food in the area where the study was conducted is based on milk, maize gruel at breakfast, maize porridge with beans and green leaves at lunch and at supper.

Further it is not clear how the complete protocol was conducted. Did they use different protocols for heart rate and blood pressure analysis of the posture response? How did they perform the deep breathing test?

The question is not clearly understood, but we assume the reviewer wants us to clarify the sequence in which the tests were conducted (page 5, paragraph 2). The same protocol was used for heart rate and blood pressure procedure. The method of the HR variation with deep breathing has been described on page 5, paragraph 4.

The statistical analysis needs some improvements. The author should consult an expert in statistics to discuss possible methods for data without normal distribution. It would be a good addition if the author could add spectral analysis of heart rate variability of this population.

Spectral analysis was not conducted in our study because a) in our study we only had access to simple equipment b) it is not relevant for resource poor settings. This is why we decided to employ the five easy-to-use tests described in our study.

Please change "baseline" to resting supine

“Baseline” has now been changed to “resting” (page 5, paragraph 6 and page 6, paragraph 4)

… delete (SD). If data are not normal a presentation of SD is not appropriate. page 7 "Because the SPSS statistical program does not facilitate adjustment for covariables in nonparametric statistics, the test results were checked using ANOVA, and each autonomic function test result was reciprocally adjusted for age and gender."

Please consult an expert in statistics. ANOVA is not the right method for data without normal distribution. You could use log transform to get an normal distribution. After data transformation you can use a parametric test.
One of the authors (GEE) is a biostatistician and has looked over the analyses once more and done some additional analyses on the results for Table 2. The concern is mainly about the deviation from normality which was observed for the 5 response measures of Table 2 and the reviewer suggests to logtransform these variables. A logtransformation is useful with right-skewed error-distribution and positive variables. After inspection of the residuals from ANOVA with factors sex and age-group and their interaction the residuals seems to deviate significantly from a normal distribution but are not right-skewed. Moreover several of the variables may attain nonpositive values making a logtransformation less useful. Nevertheless, we have redone the analyses with logtransformed responses adding first a constant to some of the variables to make them positive. The results with respect to statistical significance were still mainly the same. Thus, we think the nonparametric results are valid and cannot be improved by logtransformations. We also think that applying the nonparametric quintiles for cut-off values on the original measurement scales are correct and easier to interpret than back-transformed values approximated by wrongly assuming normality for the logtransformed variables. A comment on this has been included in the revised manuscript. See comments made in the manuscript on page 6, paragraph 1, page 7, paragraph 1.

SD has not been deleted since we still present data with mean values, but does editor still advise us to delete SD we will do so.

We thank the reviewers for their useful comments, and hope you find that with the revisions we have made, the manuscript can now be recommended for publication.

We look forward to hearing from you.

Yours sincerely,

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